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Aging-related tau astrogliopathy (ARTAG): harmonized evaluation strategy

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Abstract

Pathological accumulation of abnormally phosphorylated tau protein in astrocytes is a frequent, but poorly characterized feature of the aging brain. Its etiology is uncertain, but its presence is sufficiently ubiquitous to merit further characterization and classification, which may stimulate clinicopathological studies and research into its pathobiology. This paper aims to harmonize evaluation and nomenclature of aging-related tau astrogliopathy (ARTAG), a term that refers to a morphological spectrum of astroglial pathology detected by tau immunohistochemistry, especially with phosphorylation-dependent and 4R isoform-specific antibodies. ARTAG occurs mainly, but not exclusively, in individuals over 60 years of age. Tau-immunoreactive astrocytes in ARTAG include thorn-shaped astrocytes at the glia limitans and in white matter, as well as solitary or clustered astrocytes with perinuclear cytoplasmic tau immunoreactivity that extends into the astroglial processes as fine fibrillar or granular immunopositivity, typically in gray matter. Various forms of ARTAG may coexist in the same brain and might reflect different pathogenic processes. Based on morphology and anatomical distribution, ARTAG can be distinguished from primary tauopathies, but may be concurrent with primary tauopathies or other disorders. We recommend four steps for evaluation of ARTAG: (1) identification of five types based on the location of either morphologies of tau astrogliopathy: subpial, subependymal, perivascular, white matter, gray matter; (2) documentation of the regional involvement: medial temporal lobe, lobar (frontal, parietal, occipital, lateral temporal), subcortical, brainstem; (3) documentation of the severity of tau astrogliopathy; and (4) description of subregional involvement. Some types of ARTAG may underlie neurological symptoms; however, the clinical significance of ARTAG is currently uncertain and awaits further studies. The goal of this proposal is to raise awareness of astroglial tau pathology in the aged brain, facilitating communication among neuropathologists and researchers, and informing interpretation of clinical biomarkers and imaging studies that focus on tau-related indicators.

Keywords

Aging; ARTAG; Tau astrogliopathy; Tau

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Introduction

Tau is a microtubule-associated protein that binds to tubulin and promotes its polymerization and stabilization into micro-tubules. Tau isoforms, ranging from 352 to 441 amino acids, are generated by the alternative splicing of exons 2, 3, and 10 of the *MAPT* gene. The six isoforms differ from each other by the presence or absence of 29- or 58-amino acid inserts in the N-terminus domain and by the presence of either three (3R tau isoforms) or four (4R tau isoforms) tandem repeat sequences of 31 or 32 amino acids [24]. Mutations in the tau gene (*MAPT*) can cause hereditary frontotemporal dementia and associate with frontotemporal lobar degeneration (FTLD) [23, 26, 51, 63]. Following the description of a disorder in one family named ‘multiple system tauopathy with presenile dementia’ [62], the term tauopathy was introduced to refer to disorders in which tau protein deposition is the predominant feature [23]. Tauopathies are characterized by the accumulation of abnormal and hyper-phosphorylated tau protein in the brain and are also classified as primary or secondary [32, 37]. Tau pathology is characterized as 3R or 4R predominant or mixed 3R + 4R type [12, 30, 32]. Primary tauopathies are grouped also as FTLD-tau and comprise Pick disease (PiD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD), neurofibrillary tangle (NFT) predominant senile dementia (NFT-dementia or “tangle-only” dementia; now included in the category of PART, see below), and globular glial tauopathy (GGT) [32, 47]. In addition, many other diseases or conditions with diverse etiology, including Alzheimer disease (AD), may be associated with tau pathology [32]. The recently introduced term ‘primary age-related tauopathy’ (PART) encompasses neuronal changes previously considered as “normal aging” as well as NFT-dementia [14]. PART is distinguished from AD, largely by the absence or scarcity of amyloid (Aβ) plaques [14]. In aged individuals sex-dependent tau pathology, developing independently from AD has been also described in the hypothalamus [16, 54, 56]. Furthermore, chronic traumatic encephalopathy (CTE) is associated with a distinctive pattern of progressive neuronal and glial tau pathology [40–42].

The introduction of the Gallyas silver stain and particularly diagnostic tau immunohistochemistry led to the identification of astroglial tau pathology in the aging brain in people with or without AD-related changes, cognitive decline or movement disorders [5, 7, 11, 21, 25, 31, 34–36, 38, 46, 57]. There have been attempts to classify these tau astrogliopathies [34], but there is lack of consensus as to how best to describe and categorize them. We recommend the term aging-related tau astrogliopathy (ARTAG) to describe the spectrum of otherwise unclassified tau immunoreactivity in astrocytes (i.e., distinct from tufted astrocytes, astrocytic plaques, ramified astrocytes, or globular astroglial inclusions) mostly in aged individuals detected by tau immunohistochemistry using phosphorylation-specific, conformation-specific, or isoform-specific (4R) anti-tau antibodies. Both ARTAG and PART affect predominantly the elderly, but PART is characterized by neurofibrillary degeneration that is largely restricted to the medial temporal lobe (MTL), basal forebrain, brainstem, and olfactory bulb and cortex [14]. PART thus describes neuronal tau pathology, while ARTAG focuses on astrocytic tau pathology. Whether PART and ARTAG belong to separate or shared pathogenic processes is unknown.

We propose a four-step approach for the morphological classification of ARTAG. We anticipate that harmonizing the nomenclature and improving consistency in documentation of ARTAG is a necessary first step for defining diagnostic guidelines that will result in progress in clinicopathological correlation and investigation of the pathogenesis of ARTAG.

Morphology of tau-immunoreactive astrocytes in primary tauopathies and CTE

The defining lesions of tauopathies are intracellular aggregates of abnormal conformers of tau, consistently detectable by immunohistochemistry for phosphoepitopes (e.g., PHF1, CP13, and AT8), as well as epitopes to conformational epitopes (e.g., Alz50 and MC1) and tau isoform-specific epitopes (e.g., 4R tau isoforms) [32]. Regardless of the tauopathy, astroglial tau inclusions are mostly 4R tau-immunopositive, although ramified astrocytes in PiD as well as occasional protoplasmic astrocytes in PSP may show 3R-tau immunoreactivity [21]. Tufted astrocytes are characteristic of PSP, and astrocytic plaques are signature lesions of CBD, while so-called ramified astrocytes have been described in PiD [15, 32]. In addition, astroglial, argyrophilic, and intracytoplasmic flame or thorn-shaped inclusions were described by Nishimura et al. in PSP [49]. Phosphorylation-dependent anti-tau antibodies are highly sensitive and label lesions that are not consistently detectable by silver impregnation methods, but may show variable ubiquitin or p62/sequestosome immunopositivity, such as the globular astroglial inclusions (GAI) of GGT [1], or the fine granular tau immunopositivity (some with ‘bush-like’ appearance) of the astrocytes of AGD [11]. Some of the variation in the morphology of the immuno-labeled structures was interpreted as representing stages of a process of aggregation and fibrillation, analogous to progression from pretangles to neurofibrillary tangles in AD [6, 11]. The concept of early-stage tau accumulation in astrocytes has also been discussed in relation to the changes in the basal ganglia in PSP [53]. Finally, subpial and subependymal clusters of astrocytic tangles have been described in CTE [41].

Overview of astrocytic tau pathologies in the aging brain

Both neuronal and glial tau pathology increases in frequency with age. The most frequent neuronal tau inclusions are neurofibrillary tangles, threads, and argyrophilic grains. Neuronal and glial inclusions resembling PSP pathology can be seen in the elderly, even without clinical evidence of PSP [17, 18, 34], but these lack the typical multisystem degeneration seen with PSP. Furthermore, tuft-shaped astrocytes have been described in a subgroup of elderly individuals, especially in association with Lewy body pathology, in a distribution resembling that of PSP [25]. Nevertheless, converging data emphasize the presence of a tau astrogliopathy that differs from tufted astrocytes or astrocytic plaques as a common finding in the elderly. Despite its high prevalence, there is a lack of consensus on whether these astroglial tau pathologies in the elderly are clinically relevant, even as a concomitant pathology that might lower an individual’s threshold for the development of clinical symptoms. Research in this field has been hampered by the variation in staining methods, tau antibodies, and the inconsistent nomenclature for astroglial tau pathologies. Importantly, hypertrophic astrocytes, as revealed by hematoxylin and eosin staining and

immunohistochemistry for glial fibrillary acidic protein and excitatory amino acid transporter 2 (EAAT2), are common in the elderly, and presumably represent a reaction to multiple types of injury. The location of such reactive astrocytes varies considerably among individuals [8, 59]. Colocalization studies have indicated that glial fibrillary acidic protein-immunoreactive reactive astrocytes are not necessarily those that are also immunoreactive for tau pathology [19].

Ikeda et al. were the first to describe tau-positive thorn-shaped astrocytes (TSA), which were similar in morphology to tau-positive astrocytes described by Nishimura et al. in PSP [49]) in the subpial or subependymal regions of the gray and white matter and frequently in the depths of gyri, as well as in the basal forebrain and brainstem, in aged individuals [27–29]. TSA may occur in multiple conditions [13]. In comparison to the tufted astrocytes of PSP, TSA showed more voluminous perinuclear cytoplasm and their processes are often thicker and shorter [27]. TSA were only occasionally found in the deep cortical layers. The authors noted that anti-ubiquitin antibodies do not label TSA. They interpreted TSA as a non-specific finding and found no relationship between the number of TSA and the severity of neurofibrillary changes. Argyrophilic, tau-positive subpial and perivascular structures were also described as common TSA [27–29].

Schultz et al. reported a high prevalence of TSA in the aged human MTL, particularly the anterior MTL, at the level of the amygdala [57]. TSA were absent in individuals under 60 years, but affected almost half of brains from those over 75 years [57]. Indeed, another study also failed to find this type of tau astrogliopathy in younger individuals [33]. Schultz et al. [57] commented that tau immunopositivity was not confined to the thorn-shaped proximal processes of astroglia, but also presented as thread-like processes in the neuropil. They found that immunolabeling with AT8 was the most sensitive for demonstrating the TSA, while silver staining was less consistent [57]. They also speculated that the preferential subpial and perivascular location could be a result of exposure to CSF or to extravasated plasma proteins due to defects in blood–brain barrier permeability commonly seen in aging and neurodegeneration [36, 57]. Interestingly, a similar distribution of TSA was reported in aged baboons [55]. A study by the MRC-CFAS group confirmed the findings of Schultz et al. and added that the TSA could be less commonly observed in the vicinity of neuronal cell bodies in gray matter areas such as amygdala and dentate gyrus [36]. Also, this study documented the 4R tau nature of TSA [36]. Variable staining for Gallyas and p62 suggest that some of these astrocytes accumulate tau in a fibrillar state [34–36, 38, 46]. Uchikado et al. also reported that the frequency of TSA increased with age and was independent of AGD [66]. All studies agree that the burden of TSA is independent of AD pathology, AGD, coiled bodies, dementia status at death, or presence of the *APOE* ε4 allele [27, 28, 36, 57, 66]. These studies, however, were limited to evaluation of the MTL and did not take account of cortical and subcortical tau astrogliopathy. Few studies reported tau immunopositivity in glial cells in AD cases with prolonged duration of the disease [5, 48, 68]. Finally, a report on NFT-dementia mentioned the presence of astrocytic tau pathology in white matter and cortex [31].

The possibility that TSA may have clinical significance was first raised by Munoz et al. [46]. They used the term “argyrophilic thorny astrocyte clusters (ATACs)” and observed them in

the frontal, temporal, and parietal cortices and in subcortical white matter in a cohort of patients with nonfluent variant of primary progressive aphasia associated with AD pathology [46]. Subsequent reports also linked TSA to symptomatology, although not all found an association of ATACs with focal neurological syndromes [9, 43]. Munoz et al. noted ATACs in the white matter without discernible changes in sections stained for myelin. ATACs did not show a consistent topographic relationship to amyloid deposits, NFTs, or reactive astrogliosis [46]. Interestingly, focal glial tauopathy, interpreted as PSP-type, associated with progressive aphasia was reported by Wakabayashi et al. [67]. These observations suggested that TSA-like astrocytes might be detected not only in a subependymal or subpial location.

A peculiar constellation of tau pathology was documented in a subset of patients with dementia [35]. The most characteristic feature was a tau astrogliopathy, which was described as diffuse granular tau immunoreactivity in astrocytic processes [35]. The study emphasized additional neuronal pathologies, including threads and diffuse neuronal cytoplasmic tau immunoreactivity (pretangle-like). A further study distinguished four different patterns based on the anatomical distribution of the tau astrogliopathy and its combination with neuronal tau pathology, characterized mostly by pretangles and scattered threads [34]: (1) medial temporal lobe type (Group I); (2) amygdala type (Group II); (3) limbic-basal ganglia-nigral type with neuronal tauopathy (Group III); and (4) hippocampus-dentate gyrus-amygdala type with neuronal tauopathy (Group IV). Some of these might represent stages of the same process whereas others might be different. Nevertheless, evaluation of tau astrogliopathy in several anatomical regions indicated that in some cases astroglial tau pathology in the elderly extends beyond the MTL to involve the frontal and parietal cortices, striatum, substantia nigra, and medulla [34]. The morphology of tau astrogliopathy in these studies, was reminiscent of that reported by Munoz et al. as ATACs [46], although extension of the immunoreactivity into the astrocytic processes was emphasized [34, 35]. Distinct accumulation of TSA in the dentate gyrus of the hippocampus was also recognized [34, 36]. Mathematical modeling of hippocampal tau immunolabeling patterns suggested that some forms of tau astrogliopathy in the elderly involve hippocampal subregions in a different pattern from that of primary tauopathies [44]. Ferrer et al. [21, 38] showed that the biochemical signature of astroglial tau pathology in the elderly in both white and gray matter differed from that of other astrocytic tau pathologies in primary tauopathies. Specifically, astroglial tau pathologies in the white matter and gray matter in aging brains were not consistently detectable using phospho-specific anti-tau antibody Ser262 or conformational tau modifications at amino acids 312–322 (MC1), or tau truncated at aspartic acid 421 (tau-C3) [21, 38].

In addition, isolated tufted astrocytes were reported in the occipitotemporal gyrus in an elderly, population-representative cohort [36], and a tauopathy with tufted, thorny, fibrous, and protoplasmic forms of astrocytic pathology was described by Beach et al. [7], in a series of cases with hippocampal sclerosis and also in a community-based study [34]. Sakai et al. [52] reported prominent subcortical white matter astrocytic tau pathology in brains from two elderly patients in whom CBD was considered. In a study on cervical spondylotic myelopathy, AT8 immunohistochemistry revealed tau-positive, neuropil threads, astrocytic foot-like perivascular or subpial structures, and glial cells with short and thick processes,

which the authors termed TSA [58]. Interestingly, prominent tau astrogliopathy may be seen in familial disorders without *MAPT* mutation [20].

In summary, tau-immunoreactive astrogliopathy in the elderly represent a spectrum of morphological abnormalities including those originally described as TSA (plump, peri-nuclear cytoplasmic immunoreactivity) and additional fine granular tau immunoreactivity extending into the astrocytic processes in the gray matter. These two morphologies can be present in the same brain. TSA may be seen in subpial, sub-ependymal, or perivascular areas, as well as in the white and gray matter, while the fine granular immunoreactivity is seen in the gray matter. Most likely, the different tau-immunoreactive astroglial morphologies in different locations in the aging brain, with or without clinical correlation, reflect different pathogenetic events. We propose the umbrella term ARTAG to encompass all of these, with or without accompanying morphological features of other neurodegenerative disorders, including PSP, CBD, PiD, GGT, PART, AD, AGD, and Lewy body pathology. Some clinicopathological studies suggest that ARTAG may present clinically with focal symptoms like aphasia when circumscribed to a smaller number of regions [46]; whereas, in cases with widespread pathology dementia with or without parkinsonism might be the clinical presentation [34, 35]. On the other hand, studies focusing only on the MTL have found no relationship between ARTAG and cognitive impairment or dementia [36].

Differential diagnosis

We provide the following operational criteria for the six well-defined tau-immunoreactive astrocytic cytopathologies seen in primary tauopathies and aging brain as follows (see comparison in Table 1; Fig. 1):

1. *Tufted astrocytes* Star-like tufts of tau-positive radiating fibers. The dense tau-immunoreactive tufts are detected in the proximal part of the astrocytic processes, often usually in a symmetrical fashion. They are localized to the gray matter (mostly basal ganglia and neocortex).
2. *Astrocytic plaques* Focal and densely tau-immunoreactive stubby dilatations of distal processes of astrocytes giving a senile-plaque-like appearance without amyloid core. They are localized to the gray matter (mostly basal ganglia and neocortex).
3. *Ramified astrocytes* Tau immunoreactivity occupying mostly the perikarya and ramifying into the cell processes usually localized to one side of the cell giving the appearance of eccentric nuclei of the astrocyte. They are localized to the gray matter and to the white matter in neocortices with severe neuronal loss.
4. *Globular astroglial inclusions* Tau-immunoreactive distinct globules (up to the size of the astroglial nucleus; 1–5 μm) and dots (1–2 μm) in the perikarya and proximal parts of astrocytic processes, found in gray matter.
5. *Thorn-shaped astrocytes* (*TSA*) Tau immunoreactivity is localized in astrocytic perikarya with extension into the proximal parts of the astrocytic processes, with

inclusions also in the astrocytic endfeet at the glia limitans around blood vessels and at the pial surface. The processes are thick and short and reminiscent of thorns. They are preferentially found at subpial and perivascular locations, as well as in the white matter and less often as clusters in the gray matter.

6. *Granular or fuzzy tau immunoreactivity in processes of astrocytes* (*GFA*) Fine granular immunoreactivity of branching processes with a few dilations of gray matter astroyctes. The perinuclear soma is densely immunore-active in most of these astrocytes.

The two major cytomorphologies of ARTAG (i.e., TSA and GFA) may accompany tauopathies or other neurode-generative disorders, but ARTAG should be distinguished from the more specific astrocytic lesions that are characteristic of primary tauopathies. To understand the frequency and relevance of ARTAG, we recommend documenting ARTAG as an additional feature in primary tauopathies. It must be noted, that the astroglial tau immunoreactivity described by Botez et al. in the amygdala of AGD [11] fits best with the GFA now included as a form of ARTAG. Indeed, astrocytic tau pathology is variably seen in AGD [22]. Therefore, it is helpful to comment whether in a case of AGD additional ARTAG is present. Furthermore, there are other tau-related disorders with astrocytic tau pathology. For instance, astrocytic tau pathology is also a component of CTE [40–42]. CTE is associated with a history of repetitive concussive or subconcussive brain trauma and is characterized by widespread accumulation of hyper-phosphorylated tau in NFTs and astrocytes, which have similarity to TSA seen in ARTAG [41]. ARTAG has features that overlap those of CTE, including the accentuation of tau pathology around small cerebral vessels and in subpial and periventricular areas. On the other hand, tau pathology, including neuronal and astroglial, in CTE is more abundant in the depths of the convexity cerebral sulci, especially in early stages [41], an aspect that has not been reported in tau astrogliopathy in the aging brain [29, 34–36, 46, 57]. It is possible that CTE pathology has been considered to be age-related astrogliopathy, especially for lesions in the MTL, which can be severely affected in more advanced stages of CTE [42]. The characteristic patchy lesions at depths of cerebral sulci were not recognized as a specific morphological feature of CTE in earlier studies. Finally, tufted astrocytes in PSP, astrocytic plaques in CBD, globular astrocytic inclusions in GGT, and ramified astrocytes in PiD are distinct from tau-immunoreactive astrocytes in the gray matter in ARTAG (see Table 1).

These observations raise the possibility that ARTAG affects distinct astrocytic populations to those in established primary tauopathies. Ikeda et al. noted that the distribution of TSA was coexistent with prominent subpial and subependymal gliosis [29]. Corpora amylacea, which are heavily invested by reactive astrocytes, also share this distribution. Importantly, these astroglial populations of the “glia limitans” share common features with fibrous astrocytes, which predominate in the white matter and subpial zone [8] and with a subset of astrocytes in the gray matter [61], where ARTAG can be also observed. In contrast, astrocytic tau pathologies in CBD or PSP involve protoplasmic astrocytes and are independent of reactive astrogliosis [19, 65]. A few studies report association of glial fibrillary acidic protein and AT8 immunore-activity not only in subpial, but also in gray matter localization of tau astrogliopathy in elderly brains [35, 36]. Protoplasmic and fibrous astrocytes differ

substantially in their glutamate uptake capabilities and capacity and have very different degrees of coupling, which are important with regard to their respective calcium wave signals, resting membrane potentials, potassium buffering, glutamate metabolism, exchange of second messengers, metabolites, and other signaling intermediates between cells [50]. In addition to these differences, reaction of astrocytes varies considerably between distinct diseases of the nervous system [60]. It is these differences that may be of pathogenetic relevance to the morphologic diversity of astrogliopathy in ARTAG.

Evaluation of ARTAG

Inconsistency in assessing, describing and documenting ARTAG has impeded research and limited our understanding of the significance of this pathology. It is not clear whether the different patterns of anatomical involvement represent a continuum or distinct abnormalities with different causes. Most previous studies have focused on the MTL, but more widespread involvement is possible [34, 35]. The relative frequency of ARTAG limited to MTL as opposed to more widespread tau astrogliopathy remains unclear. Potential etiologies are not known, although defective function of the blood–brain barrier [57], metabolic encephalopathy, neurodegenerative pathologies, hypoperfusion associated with aging, AD, or vascular dementia [39, 64], and even repeated minor trauma with possible genetic risk factors may play a role. Clinical, imaging and neuropathological data related to these aspects need to be documented precisely to allow a better understanding of the pathogenesis of ARTAG [47]. A method is needed to describe morphologies that can be widely accepted and reproducible. As silver impregnation methods are difficult to standardize and immunohistochemistry for ubiquitin and p62 does not demonstrate all forms of tau cytopathology, optimal characterization of ARTAG requires the use of immunohistochemistry for phosphorylated tau. The most widely used phosphorylation-dependent anti-tau antibodies that have allowed characterization of ARTAG to date include: AT8 (pSer202/Thr205; available from different commercial sources), CP13 (Ser202; Peter Davies, Litwin-Zucker Research Center for The Study of Alzheimer’s Disease and Memory, Manhasset, NY, USA) and PHF-1 or AD2 (Ser396/Ser404; Peter Davies, NY, USA for PHF-1 or commercial sources for AD2s). Other antibodies that may prove useful in the characterization of ARTAG include those specific for tau phosphorylated at Thr181, Ser202, Ser214, Ser396, Ser422, N-terminus region epitope-specific, 4R tau isoform-specific, and some conformation-dependent antibodies such as Alz50 (but not MC-1) [21, 35, 38].

Recommendations for sampling and staining are as follows:

- Preliminary screening for ARTAG should include tau immunohistochemistry (antibodies AT8, CP13, AD2 or PHF-1 are recommended) on two sections representative of the MTL (i.e., amygdala and hippocampus at the level of the lateral geniculate body). These regions are vulnerable to TSA and GFA.
- If tau astrogliopathy is noted in the screening section, a systematic characterization of ARTAG will require analysis involving additional areas of the frontal, parietal, lateral temporal, and occipital cortices, as well as anterior and posterior portion of the basal ganglia, thalamus, midbrain at the level of substantia nigra, pons at the level of locus coeruleus, and medulla oblongata.

- In cases where focal cortical symptoms are reported, further cortical areas corresponding to the clinical symptoms or signal alterations detected in MRI should also be evaluated.

ARTAG should be considered when detecting either or both of the two cytomorphologies: TSA or GFA. As such, we propose the following four-step characterization TReSS algorithm (Table 2): *T*ype? *Re*gional involvement? *S*everity? *S*ubegional involvement?

- *First* Identify the morphologic and distribution types of ARTAG based on parenchymal localization of TSA and GFA (note that combination of these types is generally the rule):

  1. *Laminar subpial TSA* (Fig. 2a) Plump perinuclear cytoplasmic tau immunoreactivity in astrocytes in subpial locations. It is important to note whether this is more pronounced in the sulcal depths in the convexity cerebral cortices, as in CTE.
  2. *Subependymal TSA* Plump perinuclear cytoplasmic tau immunoreactivity in astrocytes in subpial or subependymal locations (Fig. 2b).
  3. *Perivascular TSA* Plump cytoplasmic immunoreactivity with tau-immunoreactive astrocytic processes around vessels (Fig. 2c) in the gray or white matter.
  4. *White matter TSA* Astrocytes in the subcortical white matter that show plump cytoplasmic immunoreactivity (Fig. 2d). Note that in the white matter these usually form small clusters (>3 astrocytes) and that it may extend into the adjacent gray matter as described for ATAC [46].
  5. *Gray matter GFA* Solitary (one or two/20× field) (Fig. 2e, f) or clustered (Fig. 2g, h) GFA (three or more/20× field) with fine granular immunopositivity of the cytoplasmic processes (GFA), with plump perinuclear cytoplasmic tau immunoreactivity. Less frequently, TSA can be also seen in the gray matter.

It must be noted that tau immunohistochemistry occasionally decorates astrocytes at the border of chronic vascular lesions in young and aged individuals. Therefore, this lesion-associated tau astrogliopathy is important to document, but is not considered an aging-related astrogliopathy.

- *Second* Identify involvement of gross anatomical regions:

  A. MTL

  B. Lobar

  C. Subcortical

  D. Brainstem

Although the most frequently involved region is the MTL, involvement of further regions should be recognized. Moreover, MTL is important for comparison with neuroim-aging data on MTL atrophy.

- *Third* Document the severity of ARTAG pathology in the region or subregion (see step four) examined. ARTAG may appear in focal clusters or in a widespread distribution. We propose documentation as to whether ARTAG involves only (1) occasional or (2) numerous astrocytes. If the latter, the focal clusters or widespread distribution should be noted. Semiquantitative scoring for ARTAG will need to be refined.
- *Fourth* Map subregional involvement to promote future exploration and scientific discovery related to ARTAG. These are the subdivisions within the gross anatomical regions of the second step and include the following (Table 3; examples are shown in Fig. 3):
  - amygdala and hippocampus, inferior temporal gyrus for MTL
  - frontal, parietal, occipital, lateral temporal (middle and superior gyrus) for lobar
  - caudate nucleus, putamen, nucleus accumbens, glo-bus pallidus, thalamus, basal forebrain for subcortical
  - mesencephalon, pons, medulla oblongata for brainstem.

It should be noted whether ARTAG is associated with features of a particular neurodegenerative disorder, or with other disease (cerebrovascular, inflammatory, metabolic, etc.) followed by the description of the type and major regional involvement.

Some examples for the diagnostic reporting are provided as follows:

1. Examples for pure types:
   a. ARTAG subpial type;

      Region: MTL;

      Subregion: hippocampus, inferior temporal cortex;

      Extent: numerous astrocytes and widespread distribution

   b. ARTAG subependymal type;

      Region: Subcortical;

      Subregion: lateral ventricle;

      Extent: occasional

2. Examples for combinations:
   (a) ARTAG gray matter type;

      Region: MTL and subcortical;

      Subregion: inferior temporal cortex and nucleus accumbens;

      Extent: numerous astrocytes in focal clusters

   plus

ARTAG white matter type;

Region: MTL;

Subregion: hippocampus, periamygdala white matter, and temporal;

Extent: numerous astrocytes with widespread distribution;

(b) ARTAG perivascular type;

Region: lobar and subcortical;

Subregion: frontal cortex and striatum;

Extent: occasional

plus

ARTAG white matter type;

Region: MTL and lobar;

Subregion: lateral temporal, frontal, and parietal lobes;

Extent: numerous astrocytes in focal clusters.

For example, the cases described by Munoz et al. [46] would be summarized in the diagnostic report as: ARTAG gray and white matter type; region: MTL and lobar; extent: numerous in focal clusters. For research purposes, the subregional involvement should be added as: gyrus ambiens, parahippocampal gyrus, fusiform gyrus, inferior, middle, and superior temporal gyri, frontal dorsolateral and orbitofrontal cortices, cingulate gyrus, and inferior parietal lobe. The cases described by Kovacs et al. [35] could be summarized as ARTAG gray matter type; region: MTL, lobar, subcortical, and brainstem; extent: numerous in focal clusters; *plus* white matter type; region: MTL; extent: numerous and widespread; with further details on the subregional involvement. The cases discussed by Santpere and Ferrer [53] as early PSP-like astrocytic changes also represent ARTAG with additional features of concomitant PSP-type pathology (i.e., cases 4 and 5).

Summary

ARTAG describes a spectrum of astroglial tau pathologies detected mainly in the elderly represented by TSA and GFA, which are distinct from astroglial lesions of primary tauopathies (i.e., tufted astrocytes, astrocytic plaques, ramified astrocytes, or globular astroglial inclusions). The frequency of ARTAG varies depending on the type: subpial, subependymal, and perivascular types are more frequent, while gray matter and cerebral white matter types might be less common. The etiology of different types might be different; however, all appear mostly associated with aging. Although documented in several publications, there is a lack of consensus on how ARTAG should be recorded and interpreted. Here we propose steps for a systematic characterization with the expectation that this will improve communication about and understanding of this condition, including its relation to other brain pathologies and clinical symptoms. This approach has the potential to help in several respects:

1. It will facilitate communication between neuropathologists and researchers. Revisiting and standardizing the terminology should help to move the field forward. It will also increase awareness of this pathology, which is under-recognized and under-studied.
2. A better differentiation of ARTAG types may help with assessing their relationship to other tauopathies. This may be particularly important in the context of CTE-related tau pathologies. Furthermore, this may help better understanding of differences in the pathogenesis of ARTAG types.
3. A regular system for typing and grading of ARTAG should facilitate comparisons between different centers, and the pooling of information in harmonized clinicopathological studies. These will potentially pave the way towards mechanistic insights and genetic studies into their pathogenesis.
4. Understanding the nature of ARTAG may help in the interpretation of clinical biomarker and imaging studies.

Development of such a common concept (Fig. 4) and nomenclature that allows comparisons across studies and aggregation of data for large-scale multi-institutional analyses is imperative in order to understand the phenomena and clinical implications of ARTAG. Future studies should also aim to re-evaluate these observations to validate this approach and to develop a concise classification of ARTAG for diagnostic neuropathology. To reach this goal, paradigms will need to be designed for ARTAG along the lines used to standardize evaluation and diagnostic criteria for tau, amyloid and α-synuclein and other major pathologies [2–4, 10, 45]. Subsequently, it will be possible to evaluate inter-rater reliability of the proposed evaluation and eventually to merge clinical and pathologic data from multiple centers to determine practical significance of ARTAG. At this preliminary stage, however, our recommendation is limited to an evaluation strategy focusing primarily on common nomenclature and classification of aging-related tau astrogliopathy.

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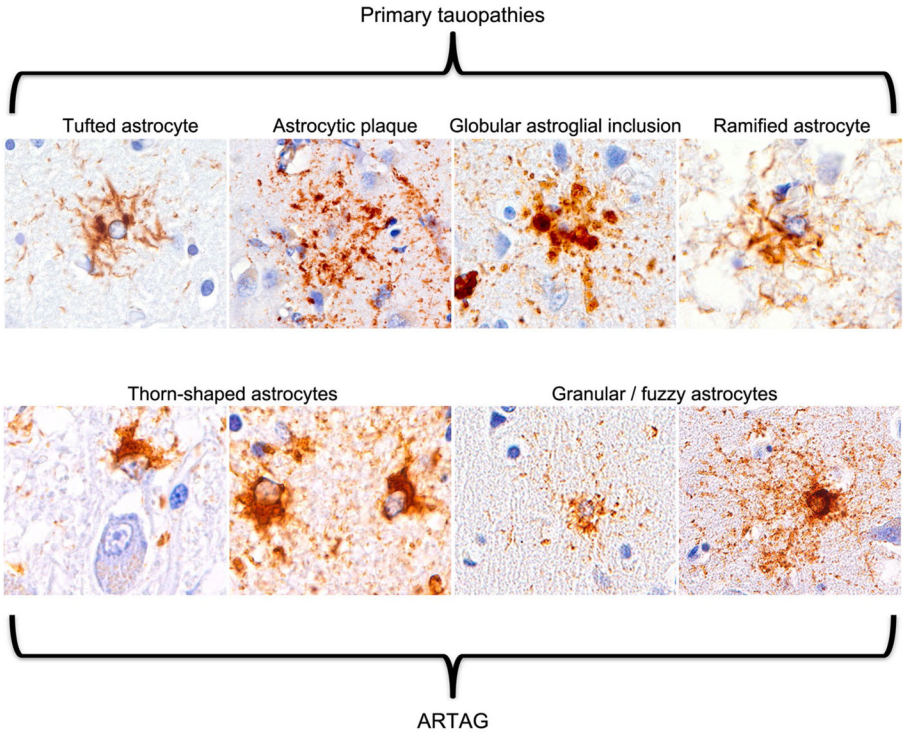

Fig. 1.

Comparison of tau (using AT8 antibody) immunoreactivities seen in primary tauopathies with those observed in aging-related tau astrogliopathy (ARTAG)

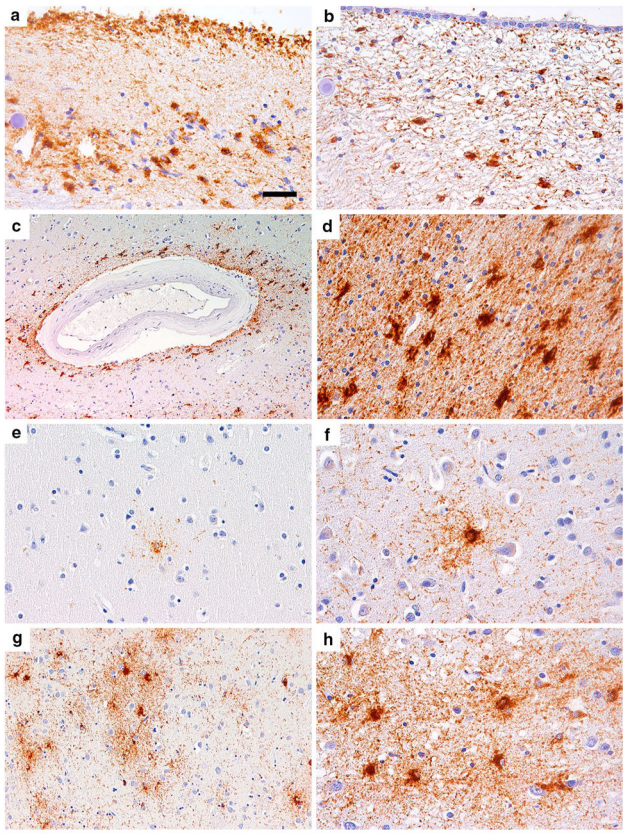

Fig. 2.

Representative photomicrographs of ARTAG types. Plump cytoplasmic tau immunoreactivity of astrocytes and tau-positive lining in subpial (**a**) and subependymal (**b**) location. Perivascular type: tau-immunoreactive astrocytic processes arranged around vessels (**c**). White matter (WM)-type: astrocytes in the subcortical white matter with plump cytoplasmic immunoreactivity (**d**). Gray matter (GM)-type: single-appearing (**e**, **f**) or clusters (**g**, **h**) of astrocytes with fine granular tau immunoreactivity in the processes without (**e**) or with (**f**) plump perinuclear cytoplasmic tau immunoreactivity. The *bar* shown in "**a**" represents 30 μm for **a**, **b**, **f**; 50 μm for **d**, **e**, **h**; and 100 μm for **c**, **g**

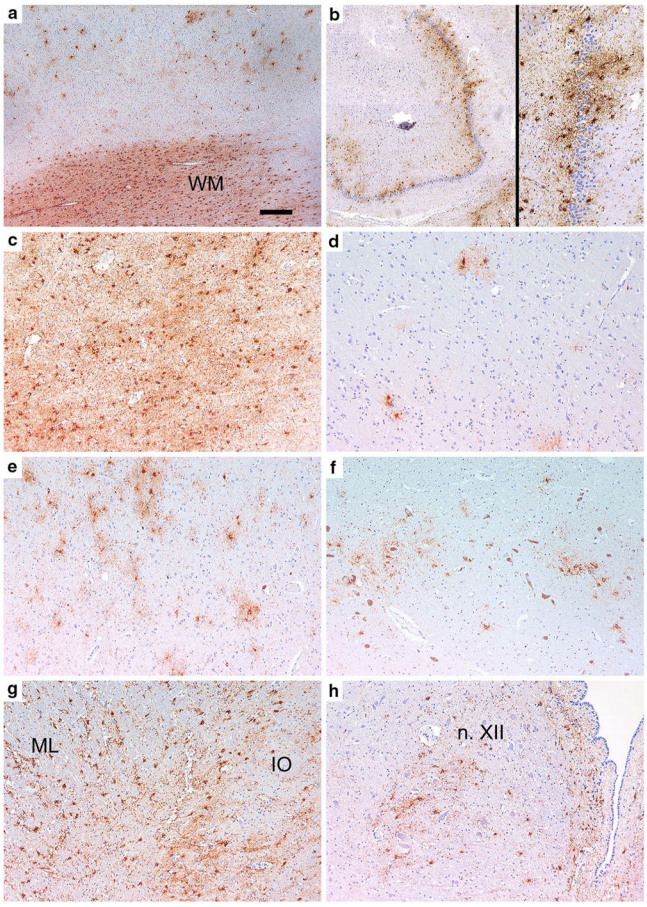

Fig. 3.

Representative images of different anatomical regions showing ARTAG. **a** Temporal cortex and white matter (WM); **b** dentate gyrus (gray matter-type cluster enlarged in the right); **c** amygdala; **d** frontal cortex (gray matter-type single); **e** nucleus accumbens (gray matter-type clusters and single forms); **f** substantia nigra; **g**, **h** medulla oblongata (*IO* inferior olive; *ML* medial lemniscus; *n. XII* hypoglossal nucleus). The *bar* shown in **a** represents 150 μm for **a**, **b**; 100 μm for the *right inset* in **b**, and **c**–**h**

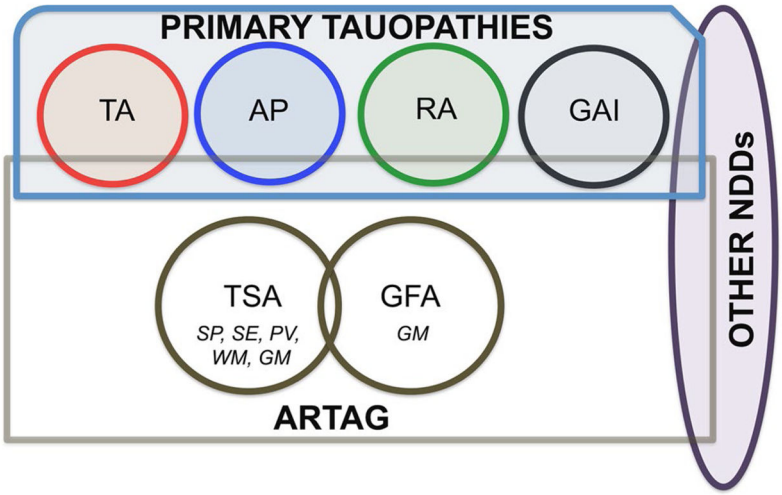

Fig. 4.

Summary of the concept of ARTAG. Four distinct astroglial tau pathologies are seen in primary tauopathies: tufted astrocytes (TA), astrocytic plaques (AP), globular astroglial inclusions (GAI), and ramified astrocytes (RA). Rarely there may be slight overlap of these morphologies, but predominance of a type is significantly associated with one of the specific primary tauopathies. ARTAG is characterized by two different morphologies: thorn-shaped astrocytes (TSA) and fine granular immunoreactivity in astrocytic processes (granular/fuzzy astrocytes: GFA); these are seen in the subpial (*SP*), sub-ependymal (*SE*), perivascular (*PV*) areas, and in the white (*WM*) and gray matter (*GM*). *TSA* and *GFA* may be present in the same brain together. Other neurodegenerative diseases (NDDs) may coexist with ARTAG or with primary tauopathies

Table 1

Operational criteria for the six well-defined tau-immunoreactive astrocytic cytopathologies seen in primary tauopathies and aging-related tau astrogliopathy (ARTAG) (see also Fig. 1)

Name	Characteristic immunoreactivity					
	Astrocytic processes					
	Soma	Proximal	Distal	Gallyas	Reported	Location
(a) Primary tauopathy-related astroglial tau pathology						
Tufted astrocytes	Relatively spared	Dense tufts: usually symmetric	No	+	PSP	GM
Astrocytic plaques	Spared	No	Stubby dilatations	+	CBD	GM
Globular astroglial inclusions	Dense: filled with globules	1–5 μm globules	1–2 μm globules	−	GGT	GM
Ramified astrocytes	Dense: localized to one side	Dense ramifications: usually asymmetric	No	+	PiD	GM, WM/GM junction
(b) ARTAG-related astroglial tau pathology						
Thorn-shaped astro - cytes (TSA)	Dense: thorn or flame shaped	Short and thick	No	−/+	With or without PSP, AGD, AD, CTE, other	GM, WM, SP, SE, PV
Granular or fuzzy astrocytes (GFA)	Dense: perinuclear accumulation	Fine or fuzzy granular	Fine granular	−/+	With or without AGD	GM

In the column “Reported” those diseases are mentioned, where there are literature reports of the specific astrocytic tau pathologies. For Gallyas silver staining: + indicates consistently detectable; −/+ indicates variably detectable (for GFA the soma may be variably positive but the processes not); - indicates usually not detectable

GM gray matter, *WM* white matter, *SP* subpial, *SE* subependymal, *PV* perivascular, *PSP* progressive supranuclear palsy, *CBD* corticobasal degeneration, *CTE* chronic traumatic encephalopathy, *PiD* Pick disease, *GGT* globular glial tauopathy, *AGD* argyrophilic grain disease

Table 2

Evaluation of aging-related tau astrogliopathy (ARTAG)

- Requires:
  - Presence of thorn-shaped astrocytes (TSA) and/or solitary or clustered astrocytes with plump cytoplasmic tau immunoreactivity that extend into the astroglial processes as fine granular immunopositivity (GFA) distinguishable from AP, TA, RA, and GAI
  - Four-step characterization of ARTAG:
    - Step 1: Distinguish types according to the location:
      - Subpial
      - Subependymal
      - Gray matter
      - White matter
      - Perivascular
    - Step 2: Describe major anatomical distribution
      - Medial temporal lobe
      - Lobar
      - Subcortical
      - Brainstem
    - Step 3: Document the severity of ARTAG
      - Occasional
      - Numerous
        - Focal
        - Widespread
    - Step 4: Map subregional involvement and extent (see Table 3)
- Ancillary studies:
  - Description of additional tau pathologies in specific anatomical regions:
    - Neurofibrillary degeneration
    - Neuropil threads
    - Diffuse cytoplasmic neuronal tau immunoreactivity (“pretangles“)
    - Argyrophilic grains
    - Dystrophic neurites around or within amyloid plaques
    - Oligodendroglial tau immunoreactivity
  - Characterization of tau phosphorylation, conformation, truncation, nitration, ubiquitination, immunohistochemistry for 4R a nd 3R tau; ultrastructural study; genetic studies (*MAPT* and other genes associated with neurodegeneration)
  - Description of concomitant neurodegenerative and non-neurodegenerative pathologies
  - Description of relation to lesions (“perilesional” astrocytic tau immunoreactivity), to corpora amylacea, and Rosenthal fibers

TSA thorn-shaped astrocyte, *GFA* granular/fuzzy astrocyte, *AP* astrocytic plaque, *TA* tufted astrocyte, *RA* ramified astrocyte, *GAI* globular astroglial inclusions

Table 3

Description of aging-related tau astrogliopathy (ARTAG) based on the type and distribution of astrocytic tau pathology

Diagnostic screening					Clinicopathological correlation and studies on pathogenesis (research)			
STEP 1		STEP 2		STEP 3	STEP 4			
Type	→	Major anatomical involvement	→	Severity	→ Detailed regional distribution and extent of ARTAG			
Subpial	→	MTL	→	occasional or numerous (focal/widespread)	→ Inf. Temporal Gy	Hippocampus	Amygdala	
		Lobar	→		→ Frontal	Parietal	Occipital	Lateral temporal
		Subcortical	→		→ Basal forebrain	-	-	
		Brainstem	→		→ Mesencephalon	Pons	Medulla obl.	
Subependymal	→	MTL	→		→ Temporal horn			
		Lobar	→		→ LV: Frontal horn	LV: Occipital horn		
		Subcortical	→		→ LV: Caudate	3V: Thalamus		
		Brainstem	→		→ Aq/Mesencephalon	Aq/Pons	Aq/Medulla obl.	
Gray matter	→	MTL	→		→ Inf. Temporal Gy	Hippocampus	Amygdala	
		Lobar*	→		→ Frontal	Parietal	Occipital	Lateral temporal
		Subcortical	→		→ Accumbens	Caud/Put	GP	Basal forebrain
		Brainstem	→		→ Substantia nigra	Pons	Medulla obl.	
White matter	→	MTL	→		→ Inf. Temporal Gy	Hippocampus	Amygdala	
		Lobar*	→		→ Frontal	Parietal	Occipital	Lateral temporal
		Subcortical	→		→ Internal capsule	Subinsular	Pencil fibers	
		Brainstem	→		→ Cerebral pedunculi	Pyramids	Midline	
Perivascular	→	MTL	→		→ Inf. Temporal Gy	Hippocampus	Amygdala	
		Lobar	→		→ Frontal	Parietal	Occipital	Lateral temporal
		Subcortical	→		→ Accumbens	Caud/Put	GP	Basal forebrain
		Brainstem	→		→ Mesencephalon	Pons	Medulla obl.	

MTL medial temporal lobe, *Gy* gyrus, *GP* globus pallidus, *Caud/Put* caudate and putamen, *Dent Gyr* dentate gyrus, *Medulla obl.* medulla oblongata, *Aq* aqueduct, *LV* lateral ventricle, *3V* 3rd ventricle

* In the case of focal cortical symptoms the anatomical area with clinical relevance should be noted additionally. Combinations of subtypes should be expected and described